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12. (a) Friedrichsen, W.; Kujath, E.; Liebezeit, G.; Schmidt, R.; Schwarz, I. *LA* 1978, 1655. (b) Friedrichsen, W.; Krüger, C.; Kujath, E.; Liebezeit, G.; Mohr, S. *TL* 1979, 237. (c) Friedrichsen, W.; Kujath, E.; Liebezeit, G. *ZN(B)* 1982, *37B*, 222. (d) Friedrichsen, W.; Schildberg, M. *H* 1983, *20*, 431.
13. Ried, W.; Nenninger, H. *S* 1990, 167.
14. Ziegler, E.; Kleineberg, G.; Meindl, H. *M* 1966, *97*, 10.
15. Kleineberg, G.; Ziegler, E. *M* 1963, *94*, 502; *M* 1965, *96*, 1353.
16. Reviews: Friedrichsen, W.; Böttcher, A.; Kappe, T. *H* 1982, *19*, 1083. Kappe, T. *Lect. Het. Chem.* 1984, *7*, 107.
17. Kappe, T.; Kos, C. *S* 1989, 629.

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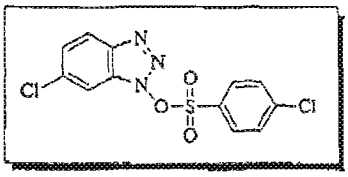
6-Chloro-1-(*p*-chlorobenzenesulfonyloxy)benzotriazole



[57320-65-7] $C_{12}H_7Cl_2N_3O_3S$ (MW 344.17)

(reagent for active ester formation;[1] synthesis of amides,[1] esters,[2] thiol esters[3] from carboxylic acids; peptide synthesis[1])

Physical Data: mp 125–127 °C.

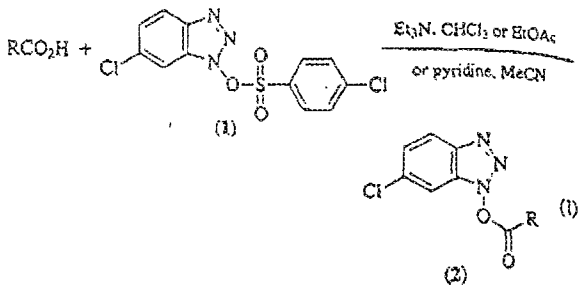
Preparative Method: prepared by reaction of 6-chloro-1-hydroxybenzotriazole with *p*-chlorobenzenesulfonyl chloride in 1M aqueous NaOH/ether.

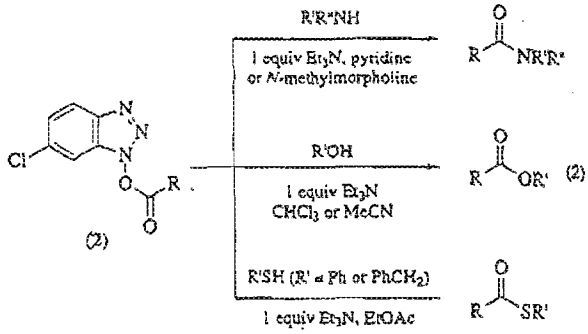
Purification: recrystallization from benzene/petroleum ether.

Handling, Storage, and Precautions: stable for long periods in the absence of moisture and light.

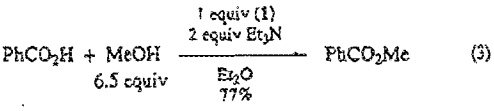
Active Ester Formation. 6-Chloro-1-(*p*-chlorobenzenesulfonyloxy)benzotriazole (1) converts carboxylic acids to the 1-acyloxybenzotriazole derivatives (2) in good yield (eq 1).[1] A study of several related reagents found (1) to be most suitable based on overall considerations of reactivity, stability, and accessibility. The reaction occurs rapidly (usually less than 1 h) in the presence of one equivalent of *Triethylamine* in $CHCl_3$ or EtOAc; the more polar solvent MeCN is required if *Pyridine* is used as base. The active esters (2) can generally be isolated as stable, crystalline solids.

The active esters (2) react readily in the presence of base with amines,[1] alcohols,[2] and certain thiols[3] to provide amides, esters, and thioesters, respectively (eq 2). Aminolysis is generally rapid, as is reaction with primary alcohols; use of secondary alcohols such as *i*-propanol requires higher temperature (boiling $CHCl_3$), while no reaction is observed between (2) and *t*-butanol.



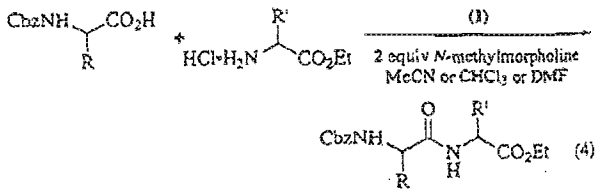


Ester formation may also be achieved without isolation of (2) by mixing a carboxylic acid and an alcohol with (1) in the presence of two equivalents of base (eq 3).[2] Formation of the 1-alkoxy-6-chlorobenzotriazole as byproduct is suppressed by the use of ether as solvent rather than $CHCl_3$; use of pyridine in MeCN is also suitable.



Similarly, one-pot amide synthesis is possible;[1] formation of sulfonamide by direct reaction of (1) with amine is avoided by using *N*-methylmorpholine or pyridine as base instead of Et_3N.[1a]

Peptide Synthesis. This method of amide bond formation has been used for peptide synthesis; the active ester is usually reacted with the amino component in situ (eq 4).[1]



These reaction conditions have advantages over the popular *1,3-Dicyclohexylcarbodiimide* (DCC) method, not least that the sulfonic acid and hydroxybenzotriazole co-products can be washed out with aqueous sodium bicarbonate. In the coupling of *N*-protected L-asparagine or L-glutamine with amino compo-

nents, no dehydration of the side-chain amide (to the nitrile) was observed. Free hydroxy or imino groups do not cause problems, as shown by the successful preparation of serine-, tyrosine- and histidine-containing peptides.

Using the coupling of Cbz-Phe-Ile-OH with H-Pro-OBn in DMF as a test, the degree of racemization using (1) with various bases was compared with other methods; less racemization occurred using (1) than with DCC.[16] A more extensive comparison of degree of racemization has also been reported.[4]

1. (a) Itoh, M.; Nojima, H.; Notani, J.; Hagiwara, D.; Takai, K. *TL* 1974, 3089. (b) Itoh, M.; Nojima, H.; Notani, J.; Hagiwara, D.; Taksi, K. *BCJ* 1978, *51*, 3320.
2. Itoh, M.; Hagiwara, D.; Notani, J. *S* 1975, 456.
3. Horiki, K. *SC* 1977, *7*, 251.
4. Kitada, C.; Fujino, M. *CPB* 1978, *26*, 585.

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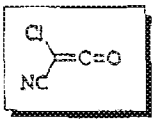
Chlorocyanoketene[1]



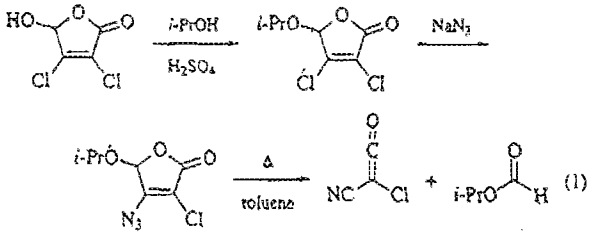
[60010-89-1] C_3ClNO (MW 101.49)

(functions as a potent electrophile in reactions with a wide variety of ketenophiles including alkenes,[3] alkynes,[4] arylaldehydes,[5] and imines[6–8])

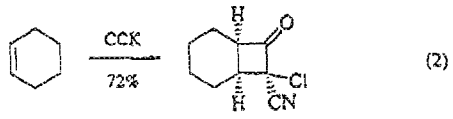
Alternate Name: CCK.

Preparative Methods: chlorocyanoketene readily undergoes self-condensation and must be generated in situ prior to usage. By generating the ketene in the presence of a ketenophile, concentration-related difficulties are circumvented and yields are greatly improved.[2] A most convenient route to the title compound is afforded by the thermal decomposition of pseudo esters of azidofuranones. Starting with commercially available mucochloric acid the desired furanone is synthesized in a two-step process: etherification and azidation (eq 1). Alcohols with at least three carbons, such as isopropanol, are desirable for the etherification in order to minimize the detonation capability of the subsequent azide.[2]

Cycloadditions to Alkenes. Cycloadditions of chlorocyanoketene (CCK) to alkenes give good yields of the corresponding cyclobutanone and include additions to di-, tri-, and tetrasubstituted alkenes. The addition process is in complete accord with a concerted $_\pi2_s + _\pi2_a$ mechanism. Cyclobutanones (1), (2), and (3) are obtained by a highly stereoselective route as evidenced by the formation of their respective single diastereomers (eqs 2–7).

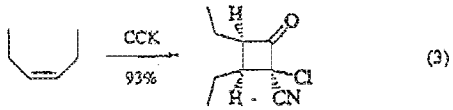


(1)



(2)

(1)



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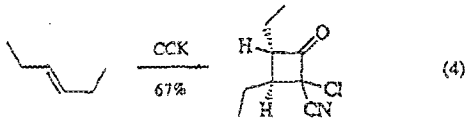

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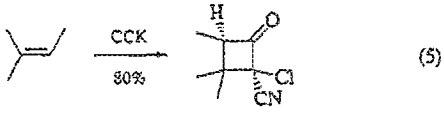
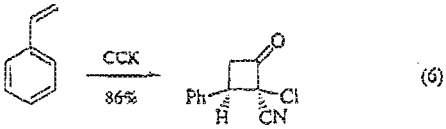


(5)

(2)



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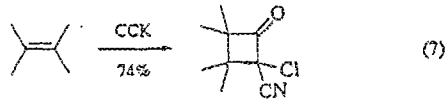
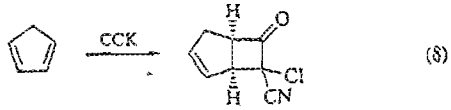
(3)



(7)

Alkenic ketenophiles with higher nucleophilic character react with CCK in a dipolar fashion. For example, treatment of cyclopentadiene with CCK gives a 55:45 mixture of diastereomers (eq 8). Further exemplifying this dipolar mode is the reaction of the ketene with dihydropyran (eq 9), whose product likely arises from a proton transfer process involving a zwitterionic intermediate.[3]



(8)